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Genetic Disorders Among Palestinian Arabs:
1. Effects of Consanguinity

Joël Zlotogora*

The Rosa and David Orzen Human Genetics Clinic, Department of Human Genetics, Hadassah Medical Center, Hebrew University, Jerusalem, Israel

Among Palestinian Arabs the rate of consanguinity is very high and some 44.3% of the marriages are between relatives (22.6% of them between first cousins). In almost 2,000 files from Palestinian Arab families who attended the genetics clinic in the Hadassah Medical Center; we were able to study the effects of consanguinity on different disorders.

The consanguinity rate in families with dominant or X-linked disorders and chromosome aberrations was similar to the one observed in the general population. We did not find any significant differences in the rate of consanguineous marriages between the parents and grandparents of children affected with trisomy 21 and the general population. Thus, we were not able to confirm the suggestion that there is an increase risk for trisomies in chidren/granchildren of consanguineous parents.

Among the parents of patients with rare autosomal recessive disorders the consanguinity rate was much higher than the one of the general population (92.5%). Among the autosomal recessive disorders, which were relatively frequent in the population, there were fewer marriages between relatives; but in most cases the difference from rare disorders is relatively small.

The importance of genetic factors in various congenital malformations, such as neural tube defects and cleft lip/palate or in various forms of infertility, was confirmed by the observation of a significantly higher consanguinity rate in the parents of these patients than is observed in the general population. Am. J. Med. Genet. 68:472–475, 1997.

KEY WORDS: Arabs; consanguinity; chromosomes; inbreeding

INTRODUCTION

Middle Eastern societies, specifically the rural Arab populations are characterized by close family relationships. The preference for marrying relatives is a deeply rooted cultural trait, and even though the major religions discourage consanguineous matings, they are very prevalent in the region. In different Middle Eastern countries the rate of consanguineous marriages varies from 23.3% to 57.9% [Khoury and Massad, 1992; Teebi, 1994]. In Israel, a study of the prevalence of consanguineous marriages among Arabs was recently performed through a written questionnaire to second-grade students from 70 different towns, villages, and cities [Jaber et al., 1994]. In 22.6% of respondents the parents were first cousins and in 44.3% the parents were related.

One possible way to study the effects of such a high rate of inbreeding on the mortality and morbidity level in the population is to compare the level of inbreeding among parents of individuals affected with different disorders to the one in the general population. We present such a study based on almost 2,000 Palestinian Arab families who visited our clinic.

MATERIALS AND METHODS

The genetic clinic opened in Hadassah Hospital in 1965 and at the end of 1995 more than 12,000 families had visited the clinic (not including those who came for routine prenatal diagnosis). This is the only genetics clinic in Jerusalem, and it serves the entire population of the region, including a part of the West Bank. In addition, the genetics clinic is a national referral center for many patients, in particular those suspected to be affected with lysosomal storage diseases.

As part of a study of genetic disorders among Palestinian Arabs in Israel we collected all the files of the Palestinian Arab families who attended the genetic clinic (almost 2,000 files). In this part of the study we recorded the degree of consanguinity between the parents of the propositi in all the cases in which a definite diagnosis was made.

In all the files a complete pedigree was available. However, it is our experience that individuals often do not know how they are related, and that first-cousin relationships are certain. Even in first-cousin marriages there are often other relations unknown to

*Correspondence to: Dr. Joël Zlotogora, Department of Human Genetics, Hadassah Hospital, POB 12000, Jerusalem, Israel 91120.

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the spouses. We distinguished between those related couples to whom no relations were known, and the couples classified here as first cousins were only at least related as such.

RESULTS

Chromosome Aberrations

In the group including the 85 patients with trisomy 21 (Table I), 40 of the parents were consanguineous (47%), 11 of them as first cousins (13%). When the same data were looked for according to the age of the mother when the affected child was born, in 27 of 56 cases (48.2%) the parents were related, 7 of them as first cousins (12.5%). When the mother was 35 years or older, in 9 of 25 cases (36%) the parents were related, 4 of them as first cousins (16%). In most cases data on the grandparents of the propositi were available and in 24 of 74 cases (32.4%) the parents of the mother were related, 15 of them as first cousins (20.2%), and in 25 of 74 cases (33.8%) the parents of the father were related, 11 of them as first cousins (14.9%).

There was a total of 118 cases of trisomy (trisomy 21 in 85 cases, other autosomal trisomies in 6, and Klinefelter syndrome in 27). Among these 118 families in which the chromosome aberration was the result of nondisjunction, the parents of the propositus were related in 53 cases (45%). Similar proportions were observed in the 37 families of propositi with other chromosome aberrations, since in 18 the parents were related. The rate of consanguinity in the whole group was 45.8% (71/155).

Monogenic Disorders

Autosomal dominant and X-linked recessive disorders. The parents were related in 14 of 29 families with autosomal dominant disorders (48.5%) and in 8 of 16 families with X-linked recessive disorders (50%).

Autosomal recessive. In this group we distinguished between disorders that were found with a relatively high frequency in our clinic and the other autosomal recessive disorders. There were 76 families with β-thalassemia (the parents of the affected individuals were related in 64 [84%]), 31 Muslim families with isolated congenital hydrocephalus (the parents of the affected individuals were related in 30 [96.5%]), 27 families with cystic fibrosis (the parents of the affected individuals were related in 24 [89%]), 27 families with familial recessive deafness (the parents of the affected individuals were related in 23 [85%]), 22 families with male pseudohermaphroditism (the parents of the affected individuals were related in 17 [77%]), and 21 families with Krabbe disease (the parents of the affected individuals were related in 16 [76%]). In 208 of 225 families with rare autosomal recessive disorders in which the diagnosis of a known and definite syndrome was made, the parents of the propositi were related (92.5%).

TABLE I. Frequency of Consanguineous Marriages in the Families of Individuals Born With Trisomy 21

Trisomy 21	Related/ total (%)	First cousin/ total (%)
All patients	40/85 (47)	11/85 (13)
Mother younger than 35	27/56 (48.2)	7/55 (12.5)
Mother 35 or older	9/25 (36)	4/25 (16)
Parents of the mother	24/74 (32.4)	15/75 (20.2)
Parents of the father	25/74 (33.8)	11/74 (14.9)

Infertility and Habitual Early Abortions (Nonchromosomal)

The group characterized by infertility and early abortions included 291 families, 116 with male infertility (in 63 the parents of the index case were related [54.5%]), 58 with female infertility (in 35 the parents were related [60.5%]), and 117 with habitual abortions (in 65 the members of the couple were related [55.5%]).

Open Neural Tube Defects

In 29 of 42 families, the parents of the propositi with open neural tube defects were related (69%). In 14 cases the open neural tube defect was anencephalus and in 2 cases it was encephalocele.

Cleft Lip/Palate and Isolated Cleft Palate

In 40 families a child was born with cleft lip/palate and in 23 of those the parents were related (57.5%). In 20 other families the child was born with isolated nonsyndromic cleft palate and in 16 the parents were related (80%).

DISCUSSION

As expected, the frequency of consanguineous marriages among the parents of individuals affected with dominant and X-linked disorders or with chromosome rearrangements was close to that observed in the general population. In a total 82 families from these three groups, the consanguinity rate was not significantly different from that of the general population (46.3% and 44.3%).

Among the rare autosomal recessive disorders the frequency of consanguineous marriages was significantly higher than in the other groups of disorders—92.5% as opposed to 44.3% in the general population. In France, where the frequency of first-cousin marriages is less than 0.2%, a study of the effect of inbreeding was performed and the highest rate of first-cousin marriages among the autosomal recessive diseases was observed for the rarest disorder studied: 12.5% of the patients with achromatopsia were offspring of first-cousin marriages (62.5 times the general population rate) [Tchen et al., 1977]. Because of the high rate of inbreeding among the Palestinian Arabs, the increase in the rate of consanguineous marriages observed in our study among the parents of patients affected with rare disorders was smaller than in the French study but still very significant (65% first cousins marriages as opposed to 22.6% in the population).

In other autosomal recessive disorders that are relatively frequent among Arabs in the region, it was expected that the rate of consanguineous marriages would be lower than for rare recessive disorders. In the study from France previously cited, the frequency of first-cousin marriages among the parents of individu-

als affected with cystic fibrosis was 1.4% versus 12.5% for a rare disorder such as achromatopsia, compared to 0.2% in the general population [Tchen et al., 1977]. In our study we observed a similar trend, but the frequency of consanguineous marriages was still very high in disorders such as thalassemia, cystic fibrosis, and recessive deafness. This may be explained by the fact that, in addition to the very high inbreeding in the population, most of the marriages are not at random. The population includes many small "isolates," and in most of the cases the marriages are within the large family (Hamula) or within the village. The high frequency of consanguinity among parents of patients affected with those disorders probably indicates that most of these cases are due to local founder effects. In only two relatively frequent recessive disorders a significantly lower rate of consanguinity was found: male pseudohermaphroditism and Krabbe disease. Male pseudohermaphroditism caused by the deficiency of 17-β-hydoxysteroid dehydrogenase was found to be frequent in Gaza where a mutation in the 17-β-hydoxysteroid dehydrogenase gene is very frequent in the whole population [Rosler et al., 1996]. The parents of the patients in our study originated mainly from the Gaza region and, as expected, the rate of consanguinity among them was lower than the one in the group of rare recessive disorders (77.2%; 41% first cousins). The high frequency of Krabbe disease in Israel is limited to three villages included in two different geographic regions [Zlotogora et al., 1991]. In each of the regions a different mutation was found, and in each case the affected child was homozygous for one of the mutations [Rafi et al., 1996]. In each of the villages the carrier frequency for Krabbe disease was calculated to be close to 10% and therefore, marriages within the village, even if the spouses are not related, has a very high risk of an affected child. This may therefore explain the relatively lower rate of consanguinity observed for the disease (76%; 57% first cousins).

In almost all cases of autosomal recessive congenital hydrocephalus the parents of the affected children were related (96.5%). This was unexpected, since the disorder is relatively frequent among Muslims (31 families), and this may suggest that congenital hydrocephalus is genetically heterogeneous in this population. Many different syndromes may lead to congenital hydrocephalus, isolated or associated with other malformations, and it may be that in fact the patients with hydrocephalus in this population were affected with different rare syndromes [Zlotogora, 1997].

A very high incidence of Down syndrome among offspring of consanguineous parents was reported by Alfi et al. [1980] in a small group of patients from Kuwait. They postulated the existence of a gene that may influence nondisjunction in the zygote or during meiosis. In our group of 85 children with trisomy 21, the consanguinity rate was similar to the one observed in the general population. When we compared the rate of consanguinity in the group of parents in which the mother gave birth to a child with trisomy 21 before the age of 35 years to the one in which the mother was older; there were no significant differences between the two groups. Similar results have been reported in several other studies and there is no support to the suggestion of an increased risk for mitotic nondisjunction in inbred communities [Basaran et al., 1992; Cereijo and Martínez-Frías, 1993]. The other possibility to explain the results of Alfi et al. [1980] is homozygosity of a recessive gene causing meiotic nondisjunction in the germ cells in one of the parents of the child with Down syndrome. In this case one would expect an increase in consanguinity among the gandparents of the child with trisomy. Analysis of our data (Table I) shows that the rate of consanguinity was similar to that of the general population in the parents of the mother and the father of the child with trisomy and that the proportion of first-cousin marriage was even lower than in the general population. Similar results were also obtained by Devoto et al. [1985] and do not support the presence of a nondisjunction gene in the populations studied.

In families with children born with neural tube defects and those with cleft lip/palate the consanguinity rate was much higher than observed in the general population (69% and 57.5%). This observation confirms the role of genetic factors in these disorders. The relatively high proportion of first cousin marriages among parents of individuals with neural tube defects (50%) suggests that some of these cases are due to monogenic disorders. In families with isolated cleft palate the rate of consanguinity was significantly higher than the one observed in multifactorial diseases. It was close to the one observed for families with autosomal recessive disorders. This may suggest that most cases of isolated cleft palate in this population are caused by genetic disorders with little influence of environmental factors.

TABLE II. Frequency of Consanguineous Marriages Among the Parents of Individuals Affected With Different Conditions

	Frequency of marriages between related individuals	
Disorders	*N*	% Age (% first cousin)
Chromosomal, total	71/155	45.8
Trisomies	53/118	45 (12.5)
Chromosomal rearrangements	18/37	48.5 (8)
Monogenic disorders		
Autosomal dominant	14/29	48.5 (27.5)
X-linked recessive	8/16	50 (19)
Autosomal recessive		
Rare	208/225	92.5 (65.5)
Thalassemia	64/76	84 (64)
Cystic fibrosis	24/27	89 (55.5)
Deafness, familial	23/27	85 (59)
Male pseudohermaphroditism	17/22	77 (41)
Krabbe disease	16/21	76 (57)
Hydrocephalus, isolated congenital	30/31	96.5 (67.5)
Neural tube defects	29/42	69 (50)
Cleft lip/palate	23/40	57.5 (27.5)
Cleft palate	16/20	80 (45)
Infertility, male	63/116	54.5
Infertility, female	35/58	60.5
Abortions	65/117	55.5 (34)
Arab population in Israel		44.3 (22.6%)

We also observed a higher rate of consanguinity among the parents of individuals with infertility than in the general population, probably in relation to the fact that many recessive disorders may cause infertility. Similar results were also obtained in the couples with recurrent abortions, probably due to the fact that genetic factors are involved in the early death of fetuses.

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